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CROI 2019: Neurologic Complications of HIV Disease

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Running Head: CROI 2019: Neurology

Abstract: *Investigators reported many new neuroHIV research findings at the 2019 Conference on Retroviruses and Opportunistic Infections (CROI). These findings included confirmation that HIV-associated neurocognitive disorder (HAND) remains common with an increasingly recognized role for comorbidities (eg, obesity) and neurodegenerative conditions (eg, Alzheimer's disease), especially as* persons living *with HIV* (PLWH) *advance into their seventh decade of life and beyond. HAND is increasingly recognized as a heterogeneous disorder that differs between individuals (eg, by sex) in the trajectory of specific neurocognitive abilities (eg, executive functioning). A more recent focus at this year's conference was toxicity* of *combination antiretroviral therapy: neurocognitive performance and neuroimaging data from several studies were presented but did not consistently support that integrase strand transfer inhibitors are associated with worse neurologic outcomes. Neuroimaging studies found that white matter changes reflect a combination of HIV and comorbidities (including cerebrovascular small vessel disease) and best correlate with blood markers of inflammation. The pathogenesis of HIV in the central nervous system (CNS) was the focus of a plenary lecture and numerous presentations on HIV compartmentalization in the CNS and cerebrospinal fluid viral escape. Novel findings were also presented on associations between HIV-associated neurologic complications and glycomics, neuron-derived exosomes, and DNA methylation in monocytes. This summary will review findings from CROI and identify new research and clinical opportunities.*

Keywords: *HIV, CROI 2019, neurology, HAND, comorbidities, neurodegenerative disorders, InSTI, central nervous system, neuroimaging, neuropathogenesis, host mechanisms*

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Introduction

The effect of HIV in the central nervous system (CNS) was an important theme of several oral and poster presentations at the 2019 Conference on Retroviruses and Opportunistic Infections (CROI). Neurologic presentations continued to focus on HIV pathogenesis and reservoirs in the CNS, persistent neurologic dysfunction (as assessed by neurocognitive testing, neuroimaging, and cerebrospinal fluid [CSF] evaluations) in virologically well-controlled persons living with HIV infection (PLWH). The role of comorbidities and their effects on brain function have become increasingly relevant as PLWH treated with ART continue to age into their seventh decade and beyond. This summary is not meant to be an exhaustive review of all material presented at CROI 2019. Instead this review concentrates on major thematic areas that may inform new avenues of research and stimulate further discussions regarding clinical management of PLWH.

HIV-Associated Neurocognitive Disorders

HIV-associated neurocognitive disorder (HAND) remains common and continues to persist despite antiretroviral therapy (ART). Within a large cohort of ART-naive PLWH who resided in Uganda, the presence of HAND at initial evaluation was associated with 68% increased odds of death at 2 years and a 98% increased odds of death within 5 years (Abstract 425). These results suggest that HAND diagnosis carries substantial morbidity and mortality risks. In the WHIS (Women's HIV Intra-agency Study) increased immune activation before the initiation of ART was associated with higher rates of neurocognitive impairment on subsequent follow-up (Abstract 407). In a cohort of individuals with acute and early HIV infection from Peru, Robertson and colleagues showed that early initiation of ART improved cognition (Abstract 445). PLWH who were recently infected (<3 months) or those individuals who initiated ART within 6 months of seroconversion, cognitive impairment improved regardless of when therapy was initiated. These results suggest that a "therapeutic window" may exist in which ART initiation might prevent the development of HAND. Overall, these results suggest that early HIV diagnosis, early initiation of therapy (especially within the first 6 months of seroconversion), and reduction of the inflammatory cascade after infection may stabilize cognitive function. The ability to identify individuals at increased risk for development of HAND is important as precision medicine through tailored therapies (eg anti-inflammatory or higher CNS penetration ART) may be beneficial for select PLWH. The diagnosis of HAND in chronically infected PLWH can fluctuate over time. De Francesco and colleagues (Abstract 420) evaluated changes in cognition

over 2 years in virologically well controlled PLWH (n=173) compared with HIV-seronegative controls individuals (n=77). At baseline evaluation, 20% of the PLWH and 3% of the HIV-seronegative individuals had cognitive impairment using a multivariate normative comparison (MNC) score. At 2-year follow-up, 13% of PLWH and 6% of the HIV-uninfected individuals had cognitive impairment based on the MNC. Although none of the cognitively impaired HIV-uninfected-participants changed over the 2-years follow-up, 46% of the PLWH improved (changed from cognitively impaired to not cognitively impaired). For those individuals who were cognitively normal at baseline, 2% of the PLWH and 4% of the HIV-uninfected participants developed cognitive impairment. Within PLWH, 10% had a reliable decline in cognition, 79% remained stable, and 11% had improved cognition. Within HIV-uninfected individuals, 7% had a reliable decline in cognition, 92% remained stable, and 1% improved. These results suggest that most PLWH who are virologically well controlled remain cognitively stable over 2 years. In contrast to other neurodegenerative disorders, in which there are progressive declines, more than half of all PLWH who have cognitive impairment at a given time point may improve over time. HAND is characterized by fluctuations in cognition over time rather than a gradual progressive decline seen in other neurodegenerative diseases. PLWH who have HAND may be considerably heterogeneous regarding the domains that contribute to neurocognitive impairment. Fitzgerald and colleagues identified distinct clusters of age-related changes in declarative memory in PLWH and HIV-uninfected individuals (n=1752) followed up in the WHIS (Abstract 408). Using a Bayesian Dirichlet process mixture model, 4 subgroups were identified: normal slow decline, normal accelerated decline, impaired accelerated decline, and impaired but stable cognition. Approximately 55% of the women had accelerated cognitive decline (both normal and impaired at baseline) that was attributable to multiple risk factors including reduced neurocognitive reserve (less education, more unemployment, and depression) and metabolic factors (obesity, diabetes, and substance use). In a cohort of PLWH and HIV-uninfected-persons followed up at the US National Institute of Health and the US Department of Defense (n=397), risk factors for worse cognitive impairment included currently smoking, history of alcohol abuse, and unemployment (Abstract 414). Overall, these results suggest that cognitive impairment seen in PLWH may reflect changes in the brain due to the virus (early in the disease) and additional risk factors (later in the disease process).

Comorbidities and HAND

Several comorbidities appear to increase the risk of cognitive impairment in virologically well-controlled PLWH. Within cohorts of PLWH at the University of California San Diego, anemia was associated with worse overall neurocognitive performance cross-sectionally and longitudinally (Abstract 426). Changes in cognition were observed in several domains including speed of information processing, motor functioning, and working memory. The authors postulate that chronic inflammation affects iron metabolism that leads to anemia. Within the HAILO (HIV Infection, Aging, and Immune Function Long-term Observational) study, gait speed and cognition were assessed in PLWH (n=929). Increased levels of hemoglobin A1C, cognitive impairment, and African American race were associated with declines in gait speed (Abstract 703). Within this HAILO group, Perez and colleagues longitudinally investigated the relationship between obesity, frailty, and cognition over time (Abstract 129). Similar to De Francesco and colleagues (Abstract 420), 78% of PLWH had no cognitive deficits and continued to have normal cognition over a 3-year interval, and 10% had cognitive impairment at both time points, 6% had an improvement in cognition at the second time point, and 6% developed impairment over the 3-year interval. Obesity and older age, but not frailty, were the greatest risk factors for developing cognitive impairment over 3 years. Finally, Chow and colleagues investigated the association between presence of cardiovascular disease (CVD) as assessed by the Atherosclerotic Cerebrovascular Disease [ASCVD] and Framingham Heart Study CVD (FRS) and risk of developing neurocognitive impairment in the HAILO cohort (Abstract 128). In unadjusted and adjusted models, higher baseline ASCVD or FRS risk score was associated with worsening in cognition over 4 years. Although the negative impact of cerebral small vessel disease (CSVD) on cognition was seen for both men and women, effects were significantly greater in women. Overall, these results point to focusing on modifiable risk factors including anemia, diabetes, and metabolic factors as intervenable targets for potentially stabilizing neurocognitive function in PLWH, especially women. Preventive interventions geared toward these comorbidities in PLWH may be important for patient care.

Neurodegenerative Diseases and HAND

A symposium presentation by Valcour focused on the potential increasing prevalence of aging-related neurodegenerative diseases in PLWH (Abstract 159). Questions remain if clinicians can successfully distinguish Alzheimer's disease (AD) from HAND and if an accelerated phenotype exists within older (>60 years old) PLWH. Inflammation persists in virologically suppressed PLWH with impairment, in the periphery (eg plasma measures) and centrally (eg positron

emission tomography [PET] measures). However, the contribution of inflammation due to virus is contentious, as a recent PET imaging study did not observe elevated neuroinflammation in virologically suppressed PLWH compared with matched HIV-uninfected persons (Abstract 460). Controversy also remains regarding whether HIV and aging accentuate or accelerate changes in brain integrity. Some studies have demonstrated a greater rate of brain atrophy in PLWH than in HIV uninfected persons and others have demonstrated that HIV and aging independently cause changes. Differences may reflect the presence of CSVD or the sample cohorts studied.

Several markers could potentially distinguish AD from HAND. PET imaging of amyloid and tau, pathological hallmarks of AD, were not abnormal in small cohorts of PLWH compared with HIV uninfected individuals. Although these studies were performed in younger PLWH, cognitively impaired individuals were included. Furthermore, if PLWH do have accelerated aging, PLWH who are 50 years old should be at increased risk for developing AD. However, the few studies that have been performed in this age range have not shown an increase in the prevalence of AD. The presence of AD in older PLWH may reflect aging and genetic risk factors and may not be specifically due to HIV. CSF amyloid and tau also serve as useful biomarkers for distinguishing AD from HAND. Conflicting results have been observed with some studies demonstrating mild alterations in CSF amyloid but not CSF tau in PLWH. Trunfio and colleagues evaluated PLWH (n=181) who were 45 years of age or older and virologically suppressed and only 1 individual (< 1%) had CSF values characteristic of AD (Abstract 415). Further longitudinal studies of neuroimaging and CSF biomarkers in older cohorts of PLWH are needed.

CNS Effects of Integrase Strand Transfer Inhibitors

Integrase strand transfer inhibitors (InSTIs) are potent components of initial ART regimens and their use is growing worldwide. With the report of more frequent neuropsychiatric adverse events (NP-AEs) in a clinical population,[1] questions have arisen about the CNS safety of InSTIs.

Several studies at CROI 2019 reported the CNS effects of initiating or switching to InSTI-containing ART. Mora-Peris and colleagues, for example, evaluated 8 PLWH who remained on a raltegravir-containing regimen and 12 PLWH who switched to a dolutegravir-containing regimen (Abstract 443). Neurocognitive performance, neuroimaging, and CSF measures were assessed at baseline and after 120 days. Although the group sizes were small, no statistically significant differences were observed between the groups in any of the assessments,

supporting the conclusion that switching to InSTI-containing ART is safe for the CNS. This conclusion was also supported by data from the Thai SEARCH (South East Asia Research Collaboration in HIV) study (Abstract 440). Participants (n=254) diagnosed with acute HIV infection had taken at least 24 weeks of ART (median, 144 weeks) and were subsequently switched to a dolutegravir-containing regimen. They were evaluated before and after the switch using multimodal assessments (neurocognitive testing, the Patient Health Questionnaire-9 (PHQ-9), major depression screening, and an assessment of distress. After switching, participants reported more somatic symptoms on the PHQ-9 and more symptoms of depression, although they only trended toward having more symptoms on the cognitive/affective subscale of the PHQ-9 and were not more likely to have evidence of moderate-to-severe depression. Importantly, no participants discontinued dolutegravir for NP-AEs and no statistically significant changes in cognitive performance or distress were observed after switching. Two other studies reported on participants who were initiating or currently taking InSTIs without an observed therapy switch. A study from Barcelona assessed participants who initiated InSTI-containing ART during early HIV infection (n=12) similar to the SEARCH study, but in contrast, compared them with those who initiated InSTI-containing ART during chronic HIV infection (n=15) and to persons without HIV (Abstract 439). In addition to a 12-test neurocognitive test battery, participants were assessed with structural neuroimaging and an assessment of daily functioning. Cognitive performance improved in all 3 groups over time and did not differ among the groups. Functional assessments identified that the early HIV infection group had evidence of greater stress levels 4 weeks after initiating ART (but was similar to other groups at 48 weeks) and that the chronic HIV infection group trended toward having worse depressive symptoms at 48 weeks. Neuroimaging identified that the chronic HIV infection group also had evidence of a reduction in medial orbitofrontal gray matter volume at weeks 4 and 48 that did not appear to be present in the other groups. Since both HIV infection groups were taking InSTI-containing ART, however, this is more likely to be due to later initiation of ART than to InSTIs specific declines.

In a cross-sectional analysis, O'Halloran and colleagues compared neurocognitive performance and neuroimaging measures in participants who were taking InSTI-containing (n=99) or non-InSTI-containing (n=103) ART (Abstract 442). The specific InSTI drugs used by participants were raltegravir (40.4%), dolutegravir (30.3%), and elvitegravir (29.3%). InSTI users had worse global neurocognitive performance (specifically in the combined learning/memory domain) than non-InSTI users and this did not appear to differ by InSTI drug (ie, the effect size for dolutegravir was similar to raltegravir and elvitegravir). Neuroimaging identified that InSTIs were associated with decreases in volumes throughout the brain. This evidence of InSTI

neurotoxicity is generally consistent with the prior report from deBoer et al,[1] but stands in contrast to other reports at CROI, and could be confounded by the cross-sectional design of the study.

Concerns about the CNS safety of InSTI drugs were also supported by in vitro and animal experiments (Abstract 435). Oligodendrocytes are not believed to be easily infected by HIV, but interest in these understudied myelin-producing glial cells is growing since white matter abnormalities are common in PLWH,[2,3] even in those taking suppressive ART, and have been linked to worse cognitive performance.[4] In carefully planned experiments, Jordan-Sciutto and colleagues administered elvitegravir or raltegravir to primary rat oligodendrocytes and monocyte-derived macrophages (MDMs, either uninfected or infected with HIV) (Abstract 435). They observed that HIV-infected MDMs inhibited oligodendrocyte differentiation but, somewhat unexpectedly, that elvitegravir (but not raltegravir) did as well. In animal experiments, investigators also induced demyelination in mice with cuprizone and found that elvitegravir inhibited remyelination. Experiments that are more mechanistic in design are being performed but these findings suggest a possible biologic basis for InSTI-associated neurotoxicity.

Other scientists reported on investigations regarding the potential neurotoxicity of other antiretroviral drugs and concomitant drugs at CROI 2019. For example, instead of focusing on switching to an InSTI-containing regimen, one study focused on the switch to tenofovir alafenamide (TAF)/ emtricitabine (FTC) from either tenofovir disoproxil fumarate (TDF)/FTC or abacavir /lamivudine (Abstract 436). Twenty PLWH were evaluated with cognitive testing and CSF assessments at 3 and 12 months after switching. No statistically significant changes were seen in cognitive performance or CSF biomarkers (neopterin, neurofilament light [NFL], β2-microglobulin, IgG index) in this small study, supporting the CNS safety of switching to TAF/FTC. In a much larger analysis, Li and colleagues aimed to determine if cognitive performance of men enrolled in the MACS (Multicenter AIDS Cohort Study) improved after discontinuing efavirenz (Abstract 441). This analysis of nearly 2,000 PLWH failed to show differences in the cognitive trajectory over time between men who either discontinued or continued efavirenz, supporting the long-term CNS safety of efavirenz. The longitudinal design and large sample size of this analysis were strengths, but an important limitation was that only 44 (2.2%) men remained on efavirenz throughout the period of observation.

DeFranceso and colleagues also focused on the CNS safety of nucleoside/nucleotide reverse transcriptase inhibitors (nRTIs) by comparing concentrations in blood of 4 nRTIs (abacavir, TDF, FTC, and lamivudine) with cognitive performance in more than 600 participants of the POPPY (Pharmacokinetic and Clinical Observations in People Over Fifty) study (Abstract

419). Population pharmacokinetic modeling estimated maximum and trough drug concentrations as well as the area-under-the-time-concentration curve. Higher concentrations of TDF and FTC were associated with worse cognitive performance in unadjusted analyses but these associations weakened above statistical significance after adjustment for potential confounding factors such as age, sex, efavirenz use, and recreational drug use. In contrast, higher abacavir concentration was associated with better cognitive performance and this association remained statistically significant even after adjustment. Although antiretroviral drugs may have neurotoxicity, they are not alone: other drug classes such as anticholinergics can also adversely affect the CNS. Published studies have reported that PLWH typically take more concomitant prescribed drugs than the general population, including drug classes with known neurocognitive adverse events (eg, Rubin et al).[5] Consistent with this, Ma and colleagues reported in cross-sectional analyses that polypharmacy, or using 5 or more concomitant drugs, was associated with worse cognitive performance (Abstract 437), particularly in learning, memory, and verbal fluency. Anxiolytics, antipsychotics, opioids, and antimicrobials were the classes of concomitant drugs that were most commonly associated with worse cognitive performance. Statistically adjusting for the underlying conditions for which these drugs were prescribed did not substantially weaken the associations, but careful longitudinal analyses are required to clearly delineate whether the observed adverse impact on the CNS is due to the underlying condition, the drug, or both.

Neuroimaging in NeuroHIV

Neuroimaging is currently not included in the evaluation for HAND, but several studies demonstrated the potential relevance of this technique in PLWH. As previously noted, CSVD may lead to vascular cognitive impairment (VCI). A combination of both CSVD and HIV may lead to the substantial cognitive changes that are observed despite ART. However, it can be difficult to differentiate the contributions of HIV from CSVD. Within the MACS, Wu and colleagues longitudinally evaluated HIV uninfected controls (n=46) and PLWH (n=76) (Abstract 456). Annualized rates of change in white matter hyperintensities (WMH), a proxy of CSVD, were similar between HIV uninfected controls and PLWH. PLWH who had diabetes or hypertension had a greater annual increase in WMH volume. Sanford and colleagues also longitudinally evaluated changes in WMH (using CSVD) in virologically suppressed PLWH (n=119) compared with HIV-uninfected persons (n=55) (Abstract 453). They also examined if an interaction occurred between CSVD and HIV for neuroimaging and cognitive measures. WMH

burden was similar for PLWH and HIV-uninfected individuals. Older age and the presence of hypertension were associated with a greater risk of an increased WMH burden. These results suggest that both HIV and CSVD may independently contribute to brain atrophy. Modifiable risk factors (eg hypertension and diabetes) should be aggressively treated in PLWH. Structural neuroimaging measurements (including magnetic resonance spectroscopy and diffusion tensor imaging) were also obtained from several cohorts of virologically suppressed PLWH. Using principal components analysis of neuroimaging data, Cysique and colleagues defined a composite neurochemical marker (CNM) or "signature of HIV disease", which strongly correlated with CSF NFL concentrations but not neurocognitive impairment (Abstract 454). Ruiz-Saez and colleagues demonstrated that perinatally infected adults living with HIV have substantial reductions in frontal brain volumes compared with matched HIV-uninfected individuals (Abstract 458). Overall, these results suggest that structural neuroimaging measures may detect changes not seen with cognitive performance testing. Observed changes may reflect neurodegeneration and inflammation that occurred soon after seroconversion and before the initiation of ART. Longitudinal neuroimaging studies of acutely infected PLWH who were administered ART are needed.

Effects of HIV on Neuropathogenesis

Many published studies have identified HIV characteristics that may influence its neurovirulence, including HIV subtype,[6,7] envelope sequence,[8,9] macrophage tropism,[10] and CD4 and chemokine receptor type 5 (CCR5) affinity.[11] These and other issues related to how HIV interacts and adapts to the brain were summarized in a plenary lecture by Swanstrom (Abstract 121). His presentation highlighted the importance for distinguishing HIV that uses R5 to enter T cells from HIV that uses CCR5 for entry specifically into macrophages (R5-macrophage tropic), which express approximately 25-times less CD4 than T-cells. He also reviewed important data supporting that approximately 25% of PLWH have evidence of compartmentalized HIV in CSF even at the time of early infection.[12] The presence of compartmentalized HIV in the CNS may be associated with viral escape from ART treatment in the CSF[13,14] (Abstract 449) and has implications for eradication of HIV from the CNS.

Several abstracts presented new data on CSF viral escape. A CSF Viral Escape Consortium was organized by the National Institute of Mental Health and proposed an approach to classify different forms of CSF viral escape.[15] Kincer and colleagues identified 14 PLWH who had one form, symptomatic CSF viral escape, and they commonly had T-cell tropic and drug-

resistant HIV in CSF (Abstract 446). Similar to the seminal report from Canestri et al in 2010,[13] nearly all participants responded to optimization of their ART regimen. Dravid and colleagues, who previously published evidence linking CSF viral escape to use of protease inhibitors,[16] reported follow-up data on CSF viral escape (n=41) after one of 2 interventions, ART optimization or intensification (Abstract 451). Intensification may be a more clinically implementable strategy since it does not require genotypic resistance testing of HIV from CSF, which is not feasible in many clinical settings. Approximately 80% of participants had suppressed CSF HIV RNA (≤20 copies/mL) with either approach. Concerns about the durability of the initial response of CSF viral escape to ART optimization were raised by Ferretti and colleagues, who identified that 5 of 21 (23.8%) PLWH with CSF viral escape who had previously responded to ART optimization had a recurrent episode of escape (Abstract 447). Recurrence only occurred, however, if the optimized regimen was simplified (n=4) or was not taken (n=1). Although CSF viral escape remains uncommon and these data are sparse, patients and clinicians should be educated to continue the optimized regimen and efforts should be made to support adherence. In addition to use of protease inhibitors, the risk of CSF viral escape has been linked to low nadir or current CD4+ cell count in chronic HIV infection. To date, no one has reported on the incidence of CSF viral escape in early HIV infection, a shortcoming that was addressed by Handoko and colleagues by analyzing data from the Thai SEARCH 010 Study (Abstract 450). Within PLWH who initiated ART during early HIV infection (Fiebig I-V) (n=89), only 1 (1.1%) met criteria for CSF viral escape at 24 weeks. Of 46 PLWH evaluated after 96 weeks of ART, none had CSF viral escape. These data add to prior evidence that initiating ART early in disease protects the CNS. Smith and colleagues identified that participants who had CSF viral escape were approximately twice as likely to have the HIV-encoded protein, Tat, detected in CSF (Abstract 417). The putative neurotoxicity of extracellular Tat remains controversial but this analysis found that participants who had a Tat concentration that exceeded 1000 pg/mL were nearly 4-fold more likely to have cognitive impairment than those who had lower concentrations. The presence of Tat in CSF was also associated with lower CSF amyloid-β 1-42 concentrations, suggesting that it may be associated with AD-type neuropathology.

In addition to these informative presentations, other scientists presented new findings relevant to how HIV interacts with the CNS. In Uganda, where non-B HIV subtypes (predominantly subtypes A and D) may affect the CNS differently than subtype B that is common in North America, Joseph and colleagues used deep sequencing to identify that 64% of PLWH (n=50) had evidence of HIV compartmentalization in the CSF (Abstract 449). The

frequency of compartmentalization did not differ by HIV subtype. Few details were provided about the cognitive assessment, but the investigators noted that CSF compartmentalization was associated with worse verbal fluency in untreated PLWH, although this difference was no longer significant after ART initiation. Oliveira and colleagues sequenced HIV envelope DNA by high-throughput single genome amplification from brain tissue collected at autopsy from 12 donors enrolled in the North American National NeuroAIDS Tissue Consortium, identifying that a third of the participants had evidence of compartmentalization compared with HIV DNA from lymph node or spleen (Abstract 452).

Measuring CSF HIV RNA down to the single-copy level may have value[17] but single-copy assays are not clinically available. The Cobas-TaqMan HIV-1 Assay v2.0 is commonly used in the clinic and has a lower limit of quantification (LLQ) of 20 copies/mL. If HIV RNA is suppressed below the LLQ, the report for this assay will indicate whether the HIV RNA concentration is ≤20 copies/mL or below the limit of detection, which may be lower than 10 copies/mL. Motta and colleagues previously identified having HIV RNA in CSF below the limit of detection is associated with lower CSF neopterin concentrations compared with having HIV RNA suppressed below 20 copies/mL.[18] At CROI, Farhadian and colleagues extended these findings to link lower HIV RNA in CSF to lower blood-brain permeability and better executive functioning. While these findings generally support that better suppression of HIV RNA, even at very low levels, may lead to better outcomes, the findings of this study may be confounded by group differences in baseline HIV RNA concentrations and nadir CD4+ T-cell counts. (Abstract 126).

Effects of Host Mechanisms on Neuropathogenesis

Even though HIV can adapt to the CNS environment, which may increase its neurovirulence, the host environment also plays a critical role, particularly among a population that is more likely than the general population to be adversely affected by comorbid conditions, such as obesity, cardiovascular disease, and drug toxicity, as discussed above. Observations from cohort studies and clinical trials are crucially important elements of translational research, but the development of clinically useful biomarkers and beneficial interventions ultimately hinges on a clear, mechanistic understanding of pathogenesis. New findings were reported at CROI 2019 that advance our understanding of the mechanisms by which the host environment increases the risk of CNS disease in PLWH.

Four presentations focused on the immune system, a key contributor to HIV pathogenesis in the CNS. One novel report focused on CD30, a CD4+ T-cell surface protein that is enriched in infected cells. Concentrations of soluble CD30 in the CSF may indicate the extent of ongoing migration of transcriptionally active T-cells during suppressive ART, although CD30 may also be solubilized from the surface of an as-yet unidentified cell type within the CNS. Peluso and colleagues measured soluble CD30 in CSF from 130 PLWH and identified that CSF, but not blood concentrations, remained elevated during suppressive ART. Higher CSF concentrations of soluble CD30 correlated with higher concentrations of NFL, an axonal protein that has been strongly linked to risk for HAND (Abstract 125). Of note, the CD30/CD30 ligand axis has been implicated in experimental autoimmune encephalitis, a disease model of autoimmune encephalitis that has some features similar to HIV encephalitis.[19] Another report from the SEARCH 010 study team built on published research about DNA methylation signatures in monocytes in HAND (particularly those associated with the nervous system and the immune response to HIV)[20] to identify that similar signatures are present in early HIV infection (median, 17.5 days after infection) (Abstract 409). Nearly a year of initiating ART, most DNA methylation changes were minimally restored except for interferon-related genes (eg, IFI27, IRF7, and MX1), suggesting that DNA methylation of these genes in blood-derived monocytes identifies HAND risk very soon after infection and might be a future, clinically accessible biomarker.

Nearly all research in the neuroHIV field is challenged by the heterogeneity of the HAND phenotype: numerous conditions contribute to HAND risk and these differ from individual to individual.[21] Chief among these differences may be sex: women and men appear to differ substantially in the conditions that predispose to impaired cognition and mental health disorders.[22] Rubin and colleagues extended their work in this area by using novel methods (Dynamic matrix factorization; Cluster Identification using Frobenius residual; Ingenuity Pathway Analysis) to analyze data from a 42-plex biomarker array measured at several time points in participants in the WIHS (Abstract 407). They found that biomarker profiles, including biomarkers classified as being associated with the antiviral immune response, oxidative stress, and vascular dysfunction within 2 years of initiating ART distinguished women living with HIV from women not living with HIV and predicted cognitive trajectory over 12 years. Among women living with HIV, biomarkers classified as “Myeloid, T Cell, and Endothelial Cell Communication” or “Microglial Chemokine-Mediated T Cell Recruitment to Brain” seemed to be broadly deleterious (as estimated by their association with performance in cognitive domains) and those classified as “Immune Activation and Vascular Dysfunction” or “Leukocyte Recruitment to Brain”

appeared be more beneficial over time. This distinction between neuropathogenic and neuroprotective mechanisms highlights an important issue in the field. To date, neuroHIV research has focused more on deleterious mechanisms associated with the neurologic complications of HIV than on mechanisms associated with resilience.

In this regard, Giron and colleagues presented very novel glycomics data, an area that has not yet been addressed in the neuroHIV field (Abstract 124). HIV causes a persistent state of hypo-sialylation that interferes with binding of sialic acid to sialic acid binding protein and that does not appear to reverse with ART. Sialyic acid binding proteins are expressed on monocytes, macrophages, and other cells and the binding of sialic acid to them may contribute to the persistent inflammation that occurs in PLWH.[23] In this initial cross-sectional analysis of participants (n=108), HIV was associated with persistent alterations in plasma and IgG glycomes, including decreases in anti-inflammatory highly-sialylated glycans, compared with controls. The investigators found that 7 glycan structures (eg, A2G3S3, LacNac Glycans) differed between participants who had cognitive impairment and those who did not. In general, maintenance of higher levels of sialylation in blood plasma was protective: higher levels of sialylated oligosaccharides correlated with better cognitive performance (or conversely, higher levels of hypo-sialylated oligosaccharides were associated with worse performance). Investigators also assessed the exosomal glycome and found that higher levels of several glycans, including α2-3 sialylated glycans, correlated with better neurocognitive performance. Data on the CSF glycome were also presented and were similar to the findings from blood. Although high-dimension, discovery-driven methods such as glycomics have limitations, the reported results are promising and strongly support the value of additional research.

In addition to the glycomic exosome work, Pulliam and colleagues presented impactful data on neuron-derived exosomes (NDEs) in blood (Abstract 411). A non-exosomal neuronal biomarker, NFL, has been measured in blood and may have clinical utility,[24] but its measurement in blood currently requires a specialized instrument (Quanterix Simoa) and its concentrations in blood can be very low during suppressive ART. In this analysis, the investigators identified sex-based differences in NDEs. In women, cognitive impairment was not associated with NFL concentrations but was associated with concentrations of 7 NDE proteins (eg, microtubule associated protein tau and neuronal cell adhesion molecule), with a consistent pattern being that the proteins were higher in women who had asymptomatic neurocognitive impairment (ANI) and lower in women with symptomatic mild neurocognitive disorder (MND). In men, the expected association between higher NFL concentrations and cognitive impairment was present but impairment was also associated with 12 NDE proteins (eg, mesencephalic

astrocyte-derived neurotrophic factor and “a disintegrin and metalloproteinase” [ADAM] metalloprotease 23) that differed from those of women and were higher in both ANI and MND than in unimpaired PLWH. Although exosome methods remain a specialized method, the prospect of identifying biomarkers of CNS neuronal injury using blood is promising and additional research is needed.

All cited abstracts appear in the CROI 2019 Abstracts eBook, available online at www.CROIconference.org.

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